Remarks/Argum nts

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 39-47 and 49-51 are pending in this application and are rejected on various grounds. Claim 50 has been amended for claim dependency. The rejection to the presently pending claims are respectfully traversed.

Priority

As discussed in the previous response, Applicants submit that the Skin Vascular Permeability assay (Example 77) has patentable utility for the PRO326 polypeptide and will clarify this point in their discussions below. These results were first disclosed in international application PCT/US98/19437, filed 17 September, 1998, support for which is found on page 52, line 26 of the PCT/US98/19437 application. Accordingly, the present application is entitled to the effective filing date of 17 September, 1998.

Double Patenting

Claims 39-44, 46-48 and 50-51 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Application No. 09/903520 (drawn to PRO335).

Applicants hereby file a terminal disclaimer compliant with 37 C.F.R. 1.321(c) to overcome this rejection. Thus, Applicants respectfully request that this obviousness-type double patenting rejection be withdrawn.

Claim Rejections – 35 U.S.C. §101 and U.S.C. §112, First Paragraph

Claims 39-47 and 49-51 remain rejected under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, allegedly for lack of specific, substantial and credible asserted utility or a well established utility. In the present Office action, the Examiner expressed that she was not clear and was somewhat confused with Applicants argument that the utility for PRO326 lies in its ability to cause inflammation. The Examiner alleged that the vascular skin permeability assay merely establishes that the applied substance is an 'irritant'. Further, the Examiner noted that the guinea pigs could be allergic to PRO326 due to presensitization to an epitope of PRO326. In a telephone interview

between Examiner Spector and Daphne Reddy, Ms. Reddy asserted that there was **no pre-sensitization** of the animal with human PRO326. Even so, the Examiner maintained that the allergic reaction could be due to prior exposure of the guinea pig to another "cross-reactive" antigen that shared an epitope with PRO326 and hence, the response could still be allergic. Finally, the Examiner points out that, based on the Rampart publication, the observation that PRO326 is an inflammatory molecule is merely a 'jumping off' point for further experimentation since Applicants did not guide a person in the art on the type of inflammation that anti-PRO326 would be useful for. Applicants respectfully traverse the above rejections.

Initially, Applicants would like to clarify that the utility for PRO326 and its variants is obviously not "to produce inflammation." As was asserted in the previous response, PRO326's utility lies in its use as a target for the development of anti-inflammatory agents (as is routinely done with other inflammatory molecules like prostaglandins, endothelins).

Regarding the Examiner's point that the observed inflammation in guinea pigs is possibly "due to an allergic reaction," Applicants strongly disagree. Only for the sake of argument, without acquiescing to this rejection, Applicants address this issue by reviewing the criteria that differentiate between an allergen and a proinflammatory molecule, and by determining which of the criteria PRO326 meets. Criteria for a qualifying proinflammatory molecule is found, again, in Rampart *et al.* (See Rampart, column 1, Abstract)) that states that a proinflammatory molecule is characterized by:

"fast onset of neutrophil accumulation, short duration (half-life of 60-70 min) and parallel plasma leakage."

The characteristics of an allergic molecule can be found in any standard immunology text book. For example, see attached excerpt (especially pg 5, 12-9) from Immunobiology by Janeway et al., (2001, Garland Publishing; Part V. The Immune System in Health and Disease, which says that an allergic molecule is characterized by:

1) an immediate IgE-mediated mast-cell activation based inflammatory response due to short-lived mediators like histamines and prostaglandins (needs prior allergen exposure), and, 2) a late-phase reaction (occurs after 8-10 hours), due to induced

synthesis and release of mediators including leukotrienes, chemokines, and cytokines from the activated mast cells (emphasis added).

In the skin vascular permeability assay, Applicants have disclosed that PRO326 caused 1) blemishes in skin (which happens due to edema or plasma leakage), and, 2) cell inflammatory responses of neutrophilic, eosinophilic, monocytic or lymphocytic cells within 6 hr (fast onset). If, as suggested by the Examiner, PRO236 were an allergen, there should not have been an accumulation of neutrophils during the immediate short phase of the reaction, since immediate allergy-associated inflammation is mast cell-mediated and is not neutrophil-mediated. Instead, the involvement of neutrophils clearly demonstrates that PRO326 meets the criteria of a proinflammatory molecule and not that of an allergen. Thus, from the "skin vascular permeability" assay results, Applicants correctly concluded that PRO326 is a proinflammatory molecule.

Further, addressing the Examiner's concerns about "the conclusion of PRO326 as an inflammatory molecule, as a "jumping off point for further experimentation" (lack of enablement)", Applicants respectfully remind the Examiner that the level of skill, knowledge and the level of predictability in the art need to be considered before determining whether the amount of experimentation is undue. In *In re Wands*, the courts concluded that the amount of experimentation needed was not undue in view of the direction and guidance provided by the Appellants and the level of skill in the art (see below).

> "the court held that ....there was 'considerable direction and guidance' in the specification; there was 'a high level of skill in the art at the time the application was filed;' and all the methods needed to practice the invention were well known." 858 F.2d at 740, 8 USPQ2d at 1406; M.P.E.P. 2164.01(a)

Applicants submit that, unlike diseases like cancer, where the mechanism of action is considered unpredictable, and which have different causative mechanisms (and thus, different molecular players) for each type of cancer, the key players and pathways associated with inflammation are few and are reasonably well understood in the art. From the data disclosed in the specification, specifically in the skin vascular permebablity assay, the skilled artisan would know that PRO326 is a proinflammatory molecule that attracts neutrophils besides other immune cells. Hence, they would know

that anti-PRO326 would be useful against inflammations that involve immune cells like neutrophils (which include acute inflammations such as lung and renal inflammation, bacterial infections, etc.). While it is true that the skilled artisan would need to conduct experiments to determine the types of inflammation that PRO326 is primarily associated with, as in the *Wands* case, such experimentation is not undue for the skilled artisan. Applicants' guidance in the present disclosure together with the existing knowledge in the art at the time of filing, which was very high, sets a pre-determined path of experimentation for the artisan to follow. Moreover, the skilled artisan in the field of anti-inflammatory therapeutics at the time of filing was very sophisticated, as evidenced by the fact that they generally possessed either an M.D. or a Ph. D or both degrees in addition to vast experience. Instead, the skilled artisan would have found it routine to evaluate the types of inflammation for which anti-PRO326 is useful.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejection – 35 U.S.C. §112-Written Description

Claims 39-43 and 50-51 were rejected under 35 U.S.C. §112, first paragraph, allegedly for lack of possession of the invention. The Examiner alleges that the claims are drawn to a genus of polypeptides defined only by sequence identity. She adds that the addition of the functional limitation was not persuasive since only a single species remained within the scope of the claims and that there was no information regarding the portions of molecules responsible for activity nor what variants were envisioned as retaining activity. Applicants respectfully traverse this rejection.

The Legal Standard

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph, is whether the disclosure "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." In re Kaslow, 707 F.2d 1366, 1375, 212 USPQ 1089, 1096 (Fed. Cir. 1983); see also Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is

to be determined on a case-by-case basis. See, *e.g.*, Vas-Cath, 935 F.2d at 1563; 19 USPQ2d at 1116. The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. Union Oil v. Atlantic Richfield Co., 208 F.3d 989, 996 (Fed. Cir. 2000).

Arguments

Whether a specification shows that Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including level of knowledge and skill in the art, and teaching provided by the specification. The inventor is not required to describe every single detail of his invention; an Applicant's disclosure obligation varies according to the art to which the invention pertains.

The present invention pertains to the field of recombinant DNA/protein technology. In particular, the invention defined by the claims concerns polypeptides having 80%, 85%, 90%, or 99% sequence identity with a polypeptide sequence and the claims also recite a functional limitation where the claimed polypeptides "induce an inflammatory response".

Further, it is well established that the level of skill in this field is relatively high, and is represented by a Ph.D. scientist having several years of experience in the pertinent field. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

Besides disclosing the full-length native human PRO326 polypeptide, the specification provides further details about the cloning and expression of variants of the polypeptide PRO326 (see, *e.g.*, pages 112-117), and the design of DNA primers for isolating associated polynucleotide (see page 185 of the specification). Additionally, the information provided from page 30 onwards refers to PRO326 as possessing leucine rich repeats, a conserved structural element, and having homology to known proteins in the leucine rich repeat superfamily such as LIG-1, ALS (see specifically

page 31, line10). Thus, structural features of the protein variants were clearly envisioned based on this disclosure. The specification further disclosed that screening methods for leucine-rich proteins were known in the art at the time of filing: "Examples of screening methods and techniques are described in the literature (see, Klein et al....; U.S. Patent No. 5,536,637), page 31, line 13. Thus, the specification provides sufficient information about structural characteristics of the variants in the genus and further demonstrates how these variants could be isolated. Thus, the skilled artisan would know that Applicants clearly had possession of the claimed polypeptides at the effective filing date.

Hence, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39780-1618 P2C27**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: February 17, 2004

By:_____
Daphne Reddy (Reg. No. 53,507)

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